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CHEMICAL EXAMINATION AND PHYSIOLOGICAL ACTION OF NUTMEG.

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The nutmeg, although considerably used as a condiment or flavoring agent, and to some extent medicinally as an aromatic stimulant, has long been known to possess a decided narcotic action when administered in any appreciable amount. The general recognition of this property is evident from the fact that it is recorded in many of the standard works descriptive of the *materia medica,* as the following few abstracts will indicate.

The "United States Dispensatory," nineteenth edition, p. 799, makes the following statement: "Nutmeg unites to the medicinal properties of the ordinary aromatics considerable narcotic power. In the quantity of two or three drachms (7.7 or 11.6 grammes), it has been known to produce stupor and delirium, and dangerous if not fatal consequences are said to have followed its free use in India." The "National Standard Dispensatory," p. 990, remarks as follows: "Nutmeg possesses aromatic, narcotic, and intoxicating properties. Given in overdose it produces stupor, decreased reflex excitability, slowness of respiration, and slight cardiac sedation." The "Pharmacographia Indica," Vol. III, p. 193, records the following information: "Mahometan doctors describe nutmegs and mace as stimulating, narcotic, digestive, tonic, and aphrodisiac." Also *Ibid.,* p. 196: "The narcotic effects of nutmegs noticed by the old

Mahometan physicians have been confirmed by Bontius, Rumphius, Lobel, Schmid, and Cullen, and more recent experiments upon man and animals agree in showing that they have a narcotic and intoxicating action. In a case related by Cullen, two drachms of powdered nutmeg produced drowsiness, which gradually increased to complete stupor and insensibility. The patient continued for several hours alternately delirious and sleeping, but ultimately recovered."

The above general statements concerning the narcotic action of nutmeg are fully confirmed by the numerous cases of "nutmeg poisoning" which have been recorded in the medical literature of more recent times, among which the following few references may be cited: *The Lancet,* April 12, 1902, p. 1035; Squibb's *Ephemeris of Materia Medica, etc.,* Vol. VII, 1904, p. 243; *The British Medical Journal,* 1906, pp. 539, 778, 900, 984; *Chem. Zeit. Rep.,* Feb. 12, 1908, p. 79, from *Deutsch. med. Wochenschrift,* 1907, Bd. 33, p. 2001; Cushny, in *Proceedings of the Royal Society of Medicine, Therapeutical and Pharmacological Section,* 1908, Vol. I, pp. 39-44.

With regard to the constituent of the nutmeg to which its narcotic effects may be attributed, the following statement in the "United States Dispensatory," nineteenth edition, p. 799, is of interest: "Dr. H. C. Wood found in experiments upon the lower animals that the oil of nutmeg is a powerful narcotic, with very much less sedative influence upon the heart than is possessed by most volatile oils. Injected into the circulation of the dog, it caused profound sleep, with slowing of the respiration, and, if the dose had been large enough, loss of reflex activity."

In the *Bericht* of Schimmel & Co., Leipzig, April, 1904, pp. 159-165, special consideration was given to the subject of nutmeg poisoning by a contribution from Dr. Fritz Jürss, Assistant at the Pharmacological Institute of the University of Rostock, entitled: "On Myristicin and some closely related substances." This comprised an account of the action of myristicin, $C_{11}H_{12}O_3$, a constituent of the essential oil of nutmeg, on frogs, fish, birds, and mammals, especially the guinea pig and rabbit. It was noted by this investigator (*loc. cit.,* p. 159) that "the oils of nutmeg and mace only cause fatal poisoning in a rabbit in doses of 10.0 to 12.0 grammes, whereas a single nutmeg (4.0 to 5.0 grammes) is capable of producing in man serious effects," and the conclusion was therefore drawn that the oil is less poisonous for animals than for man. It should be considered, however, in this connection that the essential oil of

nutmeg is very variable in character, and that some specimens may be practically free from myristicin, or even consist entirely of terpenes (compare *Ber. d. deutsch. chem. Ges.*, 1890, **23**, p. 1804). The experiments of Jürss on birds and mammals were conducted by the subcutaneous injection of myristicin, in amounts varying from 2 c.c. to 6 c.c. per kilo of bodyweight in the case of guinea pigs, or 0.9 c.c. to 1.76 c.c. per kilo of bodyweight in the case of rabbits. The effects were manifested by a paralysis of the central nervous system, with a reduction of temperature, followed by death without convulsions. A post-mortem examination of the animals showed, among other phenomena, extensive degenerative changes in the liver, such as coagulative necroses, vacuolation of the protoplasm, and the abundant presence of fat, resembling the effects of phosphorus poisoning.

Although the above-noted experiments afford ample evidence that myristicin is a substance possessing a considerable degree of physiological activity, it is also evident that the results are hardly comparable with the symptoms produced in man by the administration of relatively small amounts of nutmeg. If, for example, two nutmegs, an amount which is known to be capable of producing serious effects in man, be considered as weighing 10 grammes, they would contain on an average not more than about 1.0 gramme of essential oil, of which a very small proportion is myristicin. On the other hand, the toxic effects produced in guinea pigs weighing 500 grammes and in rabbits weighing from 1300 to 2200 grammes respectively were obtained by the subcutaneous injection of myristicin in amounts many times greater than are contained in two nutmegs, and even considerably exceeding the total amount of essential oil contained in the latter (compare also *Semi-annual Report* of Schimmel & Co., Leipzig, Oct., 1904, p. 103). From a consideration of these facts, it appeared possible that the narcotic effects produced in man by the nutmeg might not be due solely to the essential oil or the myristicin contained therein, and it was, therefore, with the object of elucidating this question that a complete study of the constituents of the nutmeg was undertaken.

Some considerable time after beginning this investigation a paper was published by Dr. A. R. Cushny (*loc. cit.*) on the subject of "nutmeg poisoning." It was noted in this communication that some years ago Dr. G. B. Wallace had undertaken an examination of the pharmacological action of nutmeg on animals and the separa-

tion of its poisonous constituent, the results having been published in 1903 in "Contributions to Medical Research," dedicated to V. C. Vaughan, Ann Arbor, Michigan. For the purpose of completeness it is desirable that the following brief abstract of the recent paper by Cushny should be included in this account of the subject.

"The nutmeg contains from 3 to 8 per cent. of volatile oil, and when this has been extracted from it the residue produces no effect whatever on animals, while small doses of the oil itself induce characteristic effects. The oil contains several terpenes and small quantities of higher boiling substances which can be separated by fractional distillation.[1] The terpenes are devoid of action except in enormous quantities, while the fraction boiling at 150° C. at 14 mm. pressure [2] proved to be a powerful poison."

Wallace conducted experiments with the high-boiling fraction of the oil on frogs, rabbits, and cats, and the following observations and conclusions drawn therefrom are further noted by Cushny, as follows:

"The cat is much more susceptible to the action than the rabbit, as is very generally the case with drugs acting on the central nervous system. About 0.4 gramme per kilo of the highest distillate given *per os* causes restlessness with weak spasmodic movements and tremor resembling that seen in carbolic acid poisoning, and profuse salivation. The restlessness passes into quiet with persistence of the tremor, incoördination of the movements, weak reflexes and partial anæsthesia. The pupils are dilated. Soon a stage of stupor, gradually deepening, sets in, the respiration is labored and feeble, and finally ceases some eight to twelve hours after the ingestion of the poison. In many cases, however, after some hours of stupor, a gradual improvement begins, and in fifteen hours from the taking of the poison the animal appears fairly normal save for unusual quietness and disinclination to move about. This improvement is only temporary, however, the cat again becoming weaker and more depressed, eating nothing and paying no attention to its surroundings, until coma returns, followed by death in 36–72 hours from the time the oil was taken."

"The symptoms in mammalia are thus, as in the frog, to be attributed to action on the central nervous system, which is depressed

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[1] Compare Power and Salway. *Journ. Chem. Soc.*, 1907, **91**, pp. 2037–2058.

[2] According to the results of our investigation of the essential oil of nutmeg (*loc. cit.*), this fraction would consist chiefly of myristicin.

for the most part, but exhibits some indication of stimulation in the form of restlessness, slight convulsive movements, and tremor. Animals, therefore, correspond very closely to man in their reactions to nutmeg poison."

"Many volatile oils induce fatty degeneration of the liver and other organs, but nutmeg poison has little or no action in this direction."

"Wallace's results do not indicate any useful purpose which nutmeg might serve in therapeutics, but are of interest in drawing attention to the possibility of serious poisoning from one of our common domestic flavoring agents."

The above record of experiments would appear to have established the fact that the narcotic properties of nutmeg are to be attributed to myristicin, and that much smaller amounts of the latter substance are required to produce the characteristic symptoms of nutmeg poisoning when administered by the mouth to a cat than when injected subcutaneously into the guinea pig or rabbit, as indicated by Jürss (*loc. cit.*). It may be noted, however, that the statement by Cushny, that nutmeg poison has little or no action in inducing fatty degeneration of the liver, is quite at variance with the observations of Jürss, and is not confirmed by the results of the experiments conducted by Dale, as recorded in the latter part of this paper.

EXPERIMENTAL.

In the beginning of this investigation it was thought possible that the narcotic action of nutmeg might be due to the presence of either small amounts of an alkaloid or of a soluble toxic protein. Special tests were therefore made for both of these classes of substances, but with negative results. For the further systematic investigation of the subject it was decided to make a complete study of (I) the essential oil, (II) the expressed oil or fat, and (III) the "press-cake" remaining after the removal of the latter, as all the constituents of the nutmeg would be included in these products.

I. *The Essential Oil of Nutmeg.*

A complete account of our investigation of this product, which was specially distilled for us from Ceylon nutmegs by Messrs. Stafford Allen & Sons, of London, has already been published (*Journ. Chem. Soc.*, 1907, **91**, 2037), and therefore need not be

specially considered here. The opportunity may, however, be taken of presenting a few comments on the requirements made for this essential oil by the United States and British Pharmacopœias.

In the "United States Pharmacopœia" (8th revision) the specific gravity of this oil was given as 0.862 to 0.910 at 25° C., and in the list of additions and corrections to June 1, 1907, these figures were altered to 0.884 to 0.924. It is evident, however, that in this alteration an error has been made, and that the limits were intended to be placed at 0.864 to 0.924 at 25° C. (compare the *Semi-annual Report* of Schimmel & Co., Leipzig, April, 1906, p. 71). The "British Pharmacopœia" requires a specific gravity of 0.870 to 0.910 at 15.5° C., the German 0.890 to 0.930, and the Belgian 0.865 to 0.920 at 15° C. The last-mentioned limits would appear to be those most in accordance with normal products of distillation.[1] In this connection it is of interest to note that the present "German Pharmacopœia" (4th edition, 1900) has adopted for the essential oil of nutmeg ("Aetherisches Muskatnussöl") the Latin title of *Oleum Macidis*. This not only involves an etymological inaccuracy, but also the assumption that the essential oils of nutmeg and mace are identical in character and composition, which has not as yet been proved to be the case. In the second (1882) and third (1890) editions of the "German Pharmacopœia" *Oleum Macidis* was correctly defined as mace oil ("Mascisöl"), and the last-mentioned title and definition have been adopted by the "Swedish Pharmacopœia" (*Pharmacopœa svecica,* ed. VIII) with the following requirements: specific gravity at 15° C. = 0.855 — 0.930; optically dextrogyrate; soluble in 3 parts of alcohol (see *Semi-annual Report* of Schimmel & Co., April, 1902, p. 73).

The "United States Pharmacopœia," in its latest edition, has introduced a requirement for oil of nutmeg, evidently adapted from the "British Pharmacopœia," which is as follows: "When 2 or 3 c.c. of oil are evaporated on a water-bath, no residue which crystallizes on cooling should be left." The purpose of this test, as stated in the "British Pharmacopœia," is to ensure the "absence of the concrete oil of nutmeg." It is likely, however, to involve the exclusion of constituents of a normal essential oil which are not without considerable value, for any crystalline residue which would be obtained from a genuine oil under these conditions would

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[1] Compare Allen and Brewis, *Pharm. Journ.*, 1901, **66**, p. 328.

consist of myristic acid, and this usually accompanies the highest boiling constituents of the oil in the process of distillation. In order, therefore, to exclude these very small amounts of myristic acid, it would be necessary that the essential oil should represent only its more volatile constituents, consisting chiefly of terpenes, and it thus becomes evident that the requirement is a thoroughly irrational one.

II. *The Expressed Oil of Nutmeg.*

This product was obtained by the expression of 23.7 kilogrammes of Ceylon nutmegs, the operation having been kindly conducted for us by Messrs. Stafford Allen & Sons, of London. An account of its complete investigation is recorded in the *Journ. Chem. Soc.*, 1908, 93, p. 1653, to which reference may be made.

III. *Examination of the "Press-cake" from Nutmeg.*

The so-called "press-cake," resulting from the expression of the above-mentioned 23.7 kilogrammes of nutmegs, amounted to about 16 kilogrammes. After being finely ground, it was mixed with purified sawdust, and successively extracted in a large Soxhlet apparatus with (A) light petroleum (b. p. 30–40° C.) and (B) alcohol.

(A.) *The Petroleum Extract.*

This consisted of a nearly colorless, solid fat, amounting to 2800 grammes, or 17.5 per cent. of the total press-cake. It was expected to contain, although in different proportions, the same substances as had previously been found by us in the expressed oil of nutmeg (*loc. cit.*), which proved to be the case.

A quantity (250 grammes) of the fat extracted by petroleum was hydrolized by heating for an hour on a water-bath with an alcoholic solution of 80 grammes of potassium hydroxide. The greater part of the alcohol was then removed, water added, and the alkaline, aqueous mixture extracted repeatedly with ether. The combined ethereal liquids were washed with a little water, dried with anhydrous sodium sulphate, and the ether removed, when about 10 grammes of a thick, yellow oil were obtained. This oil, when treated with an equal volume of dilute alcohol, deposited a small amount of a solid, which was collected, and crystallized from a mixture of

alcohol and ethyl acetate. Colorless leaflets were thus obtained, which melted at 134–135° C., and afforded the color reactions characteristic of the phytosterols.

After removing the alcohol from the liquid from which the phytosterol had originally been deposited, the residual oily product was distilled under a pressure of 10 mm., and fractions collected which boiled between 70–200° and 200–280° C./10 mm. respectively. The first of these fractions consisted of a mixture of various constituents of the essential oil of nutmeg, while the second fraction, on redistillation, boiled for the most part at 270–274° C./10 mm., and, at the ordinary temperature, formed a yellow, transparent, extremely viscid liquid, which showed no tendency to crystallize. On analysis it gave the following result:

0.2523 gave 0.6274 CO_2 and 0.1546 H_2O. $C = 67.8$; $H = 6.8$
$C_{18}H_{22}O_5$ requires $C = 67.9$; $H = 6.9$ per cent.

This substance was evidently identical with the compound $C_{18}H_{22}O_5$, which had previously been isolated from the expressed oil of nutmeg, and was fully described in connection with the latter product (*loc. cit.*). It possessed no apparent physiological activity.

The Fatty Acids.—The alkaline liquid from which the unsaponifiable material had been removed, as above described, was acidified with sulphuric acid and distilled with steam, but the distillate only contained a small amount of myristic acid. The contents of the distillation flask were then extracted with ether, the ethereal solution being washed, dried, and the ether removed. A quantity of fatty acids was thus obtained, which was distilled under 15 mm. pressure, when more than 90 per cent. of the material passed over at 196–197°, the remainder distilling from 197–240° C./15 mm. The portion boiling at 196–197° C./15 mm. melted at 54° C., and was found to consist of pure myristic acid.

0.5087 required 4.45 c.c. $\frac{N}{2}$ KOH for neutralization.
Acid value = 245.
$C_{14}H_{28}O_2$ requires an acid value of 246.

The fraction 197–240° C./15 mm. was only small in amount and contained some unsaturated acid, since it absorbed bromine in chloroform solution. On digesting it with alcohol it deposited a

very small quantity of a solid substance. The latter, after recrystallization from hot alcohol, melted at 74–75° C., and was identified as cerotic acid, which had previously been isolated by us from the expressed oil of nutmeg.

(B.) *The Alcohol Extract.*

This was a dark brown mass, amounting to 2300 grammes, or about 14.4 per cent. of the total press-cake. It was mixed with water, and the mixture distilled with steam until all the volatile substances present had been removed.

Volatile Constituents of the Alcohol Extract.

The aqueous distillate, which contained some oil floating on the surface, was extracted with ether, the ethereal solution being washed with a little water, dried with calcium chloride, and the ether removed. A quantity (about 26 grammes) of a pale yellow oil was thus obtained, which possessed an aromatic, and also somewhat pungent odor. Its density was 0.9362 at 20° C., and the optical rotation $+ 2° 59'$ in a 100 mm. tube. The presence of furfural was indicated by the odor, and by the production of a deep red color when tested with aniline in acetic acid solution.

The essential oil was first extracted with a 10 per cent. solution of sodium carbonate. This removed about 1 gramme of a solid substance which, after recrystallization from alcohol, melted at 53–54° C., and was identified as myristic acid. The oil was subsequently extracted with a 5 per cent. solution of sodium hydroxide. On acidifying the alkaline liquid, and extracting with ether, a small quantity (about 0.5 gramme) of an oil was obtained which possessed a strong odor of eugenol, and yielded a crystalline benzoyl derivative melting somewhat indefinitely between 84 and 98° C. This phenolic product evidently consisted of a mixture of eugenol and *iso*eugenol, these substances having previously been identified by us as constituents of the essential oil of nutmeg (*loc. cit.*).

After the above treatment the oil was distilled under the ordinary pressure. It commenced to pass over at 190° C., the temperature gradually rising to 265° C. The amount of this essential oil was much too small for a complete examination, and it would naturally be expected to contain the same substances as had previously been

identified in the normal product obtained by the direct distillation of nutmegs. The last portions of the distillate were, however, specially tested for myristicin, the presence of which was established by the formation of the crystalline bromo-derivative, melting at 128–129° C.

The aqueous distillate, from which the essential oil had been removed by extraction with ether, as above described, had an acid reaction. It was therefore neutralized with baryta, and the solution concentrated, when three successive crops of crystals were obtained, amounting in all to 4 grammes. Each of these barium salts, after drying at 110° C., was analyzed, with the following results:

(*a*) 0.3787 of salt gave 0.3388 $BaSO_4$. Ba = 52.6
(*b*) 1.2626 " " 1.1381 $BaSO_4$. Ba = 53.0
(*c*) 1.0017 " " 0.9040 $BaSO_4$. Ba = 53.1
$(C_2H_3O_2)_2$ Ba requires Ba = 53.7 per cent.

It is thus evident that the volatile acid consisted chiefly of acetic acid.

Non-volatile Constituents of the Alcohol Extract.

After the removal of the volatile substances by distillation with steam, as above described, there remained in the distillation flask a reddish-brown, aqueous liquid (α) and a large quantity of a very dark colored resin (β). The latter was separated and thoroughly washed with water, the washings being added to the aqueous liquid.

Examination of the Aqueous Liquid (α).

The aqueous liquid, together with the washings from the resin, was concentrated to a convenient bulk. It was first tested for the presence of an alkaloid, but, as in the previously mentioned preliminary test with powdered nutmeg, the result was negative. The liquid was subsequently extracted several times with ether, the combined ethereal liquids being washed, dried, and the ether removed, when about 20 grammes of a semi-solid, dark colored, resinous substance was obtained. This was redissolved in ether, and the ethereal liquid extracted successively with solutions of sodium carbonate and sodium hydroxide, but this treatment removed only

substances of a resinous character. The ethereal liquid was finally washed until free from alkali, and the ether removed, when about 0.5 gramme of a solid substance was obtained. The latter, after recrystallization from alcohol, melted at 54° C., and was identified as trimyristin.

The aqueous liquid, after extraction with ether, was treated with a solution of basic lead acetate, which yielded a voluminous brown precipitate. The latter was collected, washed, suspended in water, and decomposed by hydrogen sulphide. On filtering the mixture a reddish-brown liquid was obtained, which, when concentrated under diminished pressure, yielded only a resinous product. It gave a deep green color with ferric chloride, and appeared to consist chiefly of tannic and coloring matters.

The filtrate from the basic lead acetate precipitate was deprived of the excess of lead by means of hydrogen sulphide, again filtered, and the liquid concentrated under diminished pressure. A large quantity (about 1000 grammes) of a thick syrup was thus obtained, but after standing for a long time it deposited nothing crystalline. It was optically inactive, contained an abundance of sugar, and readily yielded an osazone which, after a few crystallizations from pyridine, melted at 212–213° C., and was evidently *d*-phenylglucosazone. A portion of the syrupy liquid was dried on prepared sawdust, and the mixture successively extracted in a Soxhlet apparatus with ether, ethyl acetate, and alcohol. The ether removed nothing, and the other solvents yielded only syrupy extracts from which nothing crystalline could be obtained. Another portion of the original syrupy liquid was heated for some time with dilute sulphuric acid, when a little furfural was produced, but there was no evidence of the presence of a glucoside.

Examination of the Resin (β).

The resinous matter which had been separated from the aqueous liquid, as previously described, formed, when dry, a black, brittle solid, and amounted to 490 grammes. It was dissolved in alcohol, and intimately mixed with purified sawdust. The mixture was then thoroughly dried, and extracted successively in a Soxhlet apparatus with light petroleum (b. p. 40–60° C.), ether, chloroform, ethyl acetate, and alcohol, when the following amounts of extract, dried at 100° C. were obtained:

Petroleum	extracted	47	grammes or	9.6	per cent.
Ether	"	66	" "	13.5	"
Chloroform	"	33	" "	6.7	"
Ethyl Acetate	"	55	" "	11.2	"
Alcohol	"	170	" "	34.7	"
		371	grammes or	75.7	per cent.

It is evident that by this treatment a considerable proportion of the original resin had been rendered insoluble.

Petroleum Extract of the Resin.

This was a soft, dark brown mass. It was dissolved in ether and the ethereal solution extracted, first with small successive portions of aqueous sodium carbonate, and afterwards with a solution of sodium hydroxide. The sodium carbonate extracts were of a dark brown color, and, when acidified, yielded soft, resinous solids. The latter were distilled under diminished pressure, when a small fraction was collected between 210 and 230° C./20 mm., which became crystalline on cooling. After recrystallization from alcohol, it melted at 52–53° C., and proved to be myristic acid. The sodium hydrate extract, when acidified, yielded a light yellow solid, which was readily soluble in hot, but not in cold alcohol, and was deposited from its hot solution in an amorphous state.

The portion of the petroleum extract which was not soluble in alkalies amounted to about 30 grammes. It was hydrolized by heating on a water-bath with an alcoholic solution of 12 grammes of potassium hydroxide. After the removal of the alcohol, water was added, and the alkaline mixture extracted with ether, the ethereal solution being washed, dried, and the ether removed. A quantity (about 5 grammes) of unsaponifiable material was thus obtained, which was distilled under diminished pressure, and the following fractions collected: 160–175°; 175–280°; 280–310° C./15 mm. Only the highest fraction, 280–310° C./15 mm., was sufficient in amount for further examination. This was a yellow, viscid product which, on digesting with dilute alcohol, yielded a very small amount of solid substance. The latter, after crystallization from a mixture of alcohol and ethyl acetate, melted at 135°, and yielded the color reactions characteristic of the phytosterols.

The above-mentioned aqueous, alkaline liquid, after extraction with ether, was acidified with sulphuric acid and distilled with steam, but the only volatile product was a little myristic acid. The contents of the distillation flask were then extracted with ether, the ethereal solution being washed, dried, and the ether removed. A quantity of solid acids was thus obtained, which was distilled under diminished pressure to remove some resinous matter. The greater portion passed over at 205° C./20 mm., and consisted of practically pure myristic acid, melting at 53° C. From a smaller fraction, collected between 205 and 250° C./20 mm., a small quantity of cerotic acid, melting at 74–76° C., was isolated. Some unsaturated acids were also present in the mixture.

Ether Extract of the Resin.

This was a soft, reddish-brown solid. It was digested with an amount of ether insufficient to dissolve the whole, and the sparingly soluble portion separately examined. This latter portion was a brownish, brittle mass, which was readily soluble in hot, but only moderately soluble in cold alcohol. It was systematically fractionated from alcohol, but the deposits all appeared to be amorphous. In order to ascertain whether a crystalline acetyl compound could be obtained from this product, it was heated with acetic anhydride and anhydrous sodium acetate for several hours. The mixture was then treated with water, when a solid substance separated, which was collected, washed with water, and dried on a porous plate. On fractionating this substance from hot alcohol, the first few deposits, representing the greater portion of the material, were quite amorphous. The mother-liquors, however, on standing for some time, yielded a small quantity (about 0.2 gramme) of a crystalline substance, which was separated from some amorphous matter by filtration through muslin. The crystalline substance was thus obtained in flat plates, melting at 163–164° C., and, after drying at 105° C., was analyzed.

0.1016 gave 0.2580 CO_2 and 0.0889 H_2O. $C = 69.3$; $H = 9.7$.

It was then recrystallized from methyl alcohol, when, after drying at 105° C., it melted at 164–166° C., and was again analyzed.

0.0706 gave 0.1798 CO_2 and 0.0596 H_2O. $C = 69.5$; $H = 9.4$

$C_{27}H_{44}O_6$ requires $C = 69.8$; $H = 9.5$ per cent.

The substance afforded a color reaction similar to that characteristic of the phytosterols. Thus, when dissolved in chloroform with a little acetic anhydride, and a drop of concentrated sulphuric acid added, a pink color was produced which rapidly changed to blue and finally to green.

The composition and character of the above-described substance render it evident that it is diacetylipuranol, $C_{23}H_{38}O_4$ $(CO.CH_3)_2$. The dihydric alcohol, ipuranol, $C_{23}H_{38}O_2$ $(OH)_2$, was first isolated in these laboratories from the resin of *Ipomœa purpurea,* Roth (*Amer. Journ. Pharm.,* 1908, **80**, p. 264), and subsequently from olive bark (*Journ. Chem. Soc.,* 1908, **93**, p. 907).

The above-mentioned ethereal solution of the more readily soluble portion of the ether resin was extracted, first with small successive portions of a saturated solution of sodium carbonate, and subsequently with a 10 per cent. solution of sodium hydroxide. The first sodium carbonate extract formed a thick, dark brown emulsion of an insoluble sodium compound which could not be filtered. It was, therefore, directly acidified, when a yellow solid was obtained, which was collected and washed with water. The attempts to obtain it in a crystalline form were unsuccessful, and it also yielded nothing crystalline on acetylation. The subsequent sodium carbonate extracts were similar in character and behavior to that above described. The sodium hydrate extracts were dark in color, and, on acidification, yielded brown, amorphous products. After extracting the ethereal solution with the above-mentioned alkalies, it was washed, dried, and the ether removed, but only a small amount of a pale yellow, amorphous product was obtained.

Chloroform, Ethyl Acetate, and Alcohol Extracts of the Resin.

The portion of resin extracted by chloroform was a reddish-brown solid, while the portions removed by ethyl acetate and by alcohol respectively were soft, black masses. Nothing of a crystalline character could be obtained from any of these products. In order to ascertain whether the alcohol extract of the resin contained anything of a glucosidic nature, a quantity (50 grammes) of it was heated for several hours in alcoholic solution with such an amount of sulphuric acid that the latter represented 5 per cent. of the mixture. After the removal of the greater portion of the alcohol, water was added, and the mixture distilled with steam. A small amount of a volatile oily product was thus obtained, which was found to contain

furfural. The distillation flask then contained a quantity (35 grammes) of a black resin, together with an aqueous liquid of a reddish color. The resinous matter was separated by filtration, and carefully examined, but nothing crystalline could be obtained from it. The filtered aqueous liquid was first extracted with ether, which, however, removed only a little amorphous coloring matter. It was then treated with an amount of baryta just sufficient for the removal of the sulphuric acid, and the filtered liquid concentrated under diminished pressure. A dark colored product was thus obtained which reduced Fehling's solution, but no osazone could be prepared from it.

In considering the results of this investigation, it may be noted that the only constituents of the petroleum and alcohol extracts from the "press-cake" of nutmeg which had not previously been identified in either the essential oil or the expressed oil were the following: sugar, tannic acid and coloring matters, resins, and a very small amount of the crystalline alcohol, ipuranol, $C_{23}H_{38}O_2(OH)_2$.

Physiological Tests.

In order to obtain confirmation of the statements which have previously been recorded that the narcotic effects produced by nutmeg are due to the essential oil or the myristicin contained therein, and also to ascertain whether any of the other products obtained in the course of this investigation possessed physiological activity, a considerable number of tests were conducted for us by Dr. H. H. Dale, Director of the Wellcome Physiological Research Laboratories. Many of these tests were performed prior to the publication of the observations by Professor Cushny on the subject of nutmeg poisoning, to which reference has been made in the introductory portion of this paper.

It was found by Dr. Dale that nutmeg itself, when administered to a cat, in doses of 5 grammes, has a very marked effect. Thus a cat weighing 2640 grammes was given 5 grammes of nutmeg at 2.30 P.M. A small amount of this was vomited during the night, but the cat seemed practically well on the following day. On the second day after administration, however, the animal was found to be very sluggish. It could walk when roused, but very quickly dropped into a semi-comatose condition, and at 3 P.M. on this day it died. Apart from a slight congestion of the intestinal mucous membrane, the only post-mortem abnormality was a fatty degenera-

tion of the liver. In another case, in which 10 grammes of nutmeg were given, no effect except slight malaise and some salivation could be observed until the third day after administration, when the cat was found in a state of very deep coma, and shortly afterward died. Another cat, to which 5 grammes of nutmeg were given, died on the morning of the fourth day after administration. The liver again showed marked fatty degeneration, and the urine contained much bile and a little albumin. The kidneys were not noticeably abnormal.

In connection with the above results it may be noted that the dog appears to be comparatively insensitive to the toxic action of nutmeg, since doses amounting to as much as 20 grammes of the substance, and even 10 c.c. of myristicin, have been given by the mouth to this animal without any perceptible effect. Injections of the essential oil and of myristicin intravenously did, indeed, cause acute symptoms of incoördination and, in some instances, complete unconsciousness; but the value of such observations is seriously diminished by the consideration that the insoluble oil will produce multiple emboli, certainly in the lungs, and possibly also in the cerebral capillaries, insofar as it passes into the lungs and gets into the general circulation. Pulmonary hemorrhage was actually the cause of death in these cases.

With regard to the action of myristicin, $C_{11}H_{12}O_3$, the high-boiling constituent of the essential oil of nutmeg, to which, in accordance with the observations of Wallace, the narcotic effects produced by nutmeg are attributed by Cushny, as also independently by Jürss (*loc. cit.*), the following experiments may be noted.

Quantities of myristicin which were appreciably greater than the amount of this substance contained in a toxic dose of nutmeg, for example, 0.1 to 0.2 c.c., when given by the mouth to a cat, produced no apparent effect. A dose of 1 c.c. of myristicin, however, produced results which were not dissimilar to those produced by 5 to 10 grammes of nutmeg. Thus a cat to which 1 c.c. of myristicin was given by the mouth survived without marked symptoms until the third day after administration, when it was found lying in a semiconscious condition. The fatty degeneration of the liver, and staining of the urine and all the tissues with bile pigment, were the only noticeable abnormalities post mortem. Another cat, to which an equal dose was given, survived until the seventh day after administration, but the changes observed post mortem were similar in character to those above described.

These results, whether produced by nutmeg itself, or by myristicin in doses up to 1 c.c. of the latter, clearly differ from the recorded effects of nutmeg on man. By the administration of rather larger doses of myristicin to the cat, some light was thrown on this discrepancy. Thus 1.5 c.c. of myristicin, given by the mouth to a cat of 3 kilogrammes, produced after a few hours a condition not unlike that described by Wallace, as reported by Cushny. The animal showed considerable excitement, together with some incoördination, and avoided obstacles imperfectly. The pupils were dilated. No actual stupor or narcosis, however, was observed, but the excitement was succeeded on the following day by a condition of unusual quietness. The second day after administration the cat became deeply jaundiced, comatose, and died. A post-mortem examination showed very advanced fatty degeneration of the liver. Another cat, to which 2 c.c. of myristicin were given, showed marked excitement and incoördination about half an hour after administration. It then became unconscious and lay narcotized for about three hours, but subsequently recovered consciousness, and the primary effects gradually disappeared. In this case again, after an interval of a day without symptoms, jaundice and coma appeared, and on the third day after administration the cat died. The primary effects—excitement, incoördination and narcosis—are not markedly different from the effects reported to be produced by nutmeg in man. Apart from the question of dosage, the difference, in any case, is not greater than that observed in other drugs affecting principally the brain. On the other hand, the remote effects of myristicin, including the terminal coma, may with considerable probability be regarded as secondary to the degenerative changes in the liver. In man the dose necessary to produce narcosis is too small to lead to these remote bad results, while in the much less sensitive cat a dose which is large enough to cause the primary cerebral symptoms causes also extensive liver changes, and is therefore ultimately fatal.

The main discrepancy between the results produced by nutmeg on the one hand and those produced by myristicin on the other is that due to dosage. It would be quite reasonable to attribute all the effects of nutmeg on the cat to myristicin, but for the fact that the dose of nutmeg sufficient to cause death in a few days represents a quantity of myristicin which, given by the mouth, produces no appreciable effect. It seems possible, however, that the discrepancy may be explained by a consideration of the conditions of absorption. Thus the failure to obtain an effect with small doses of myristicin

may be due to its being only imperfectly absorbed when given in a pure state, and passing out to a large extent in the fæces. A small dose of myristicin might, therefore, be expected to be effective if injected hypodermically, for although the absorption of such a substance from the subcutaneous tissue would be very slow, none at least would leave the body without passing through the circulation. It was found, in fact, that a dose of 2 minims (about 0.12 c.c.) of myristicin, when injected hypodermically into a cat, produced a very slow, but ultimately extensive degeneration of the liver, the latter effect being manifested during life by wasting and jaundice. This slow degeneration is what might be expected when a substance so sparingly soluble as myristicin has to be absorbed from the connective-tissue spaces.

The other products from nutmeg which were subjected to physiological tests comprised the following:

1. A *viscid substance,* boiling at 270–280° C. under 15 mm. pressure, and agreeing in composition with the formula $C_{18}H_{22}O_5$, which was separated from the unsaponifiable constituents of the expressed oil of nutmeg (*loc. cit.*).

2. The *resins* obtained from the "press-cake."

3. The *aqueous liquid* obtained, as described in this paper, from the alcoholic extract of the "press-cake," after the separation of the resins.

The viscid substance (1) was given to a cat in doses of 0.5 and 1.0 gramme respectively, but no physiological effect could be observed. The resins (2) and the aqueous liquid (3) likewise produced no noticeable effects when administered in amounts corresponding to many times the toxic dose of nutmeg. All these products must therefore be regarded as physiologically inactive.

With consideration of the results above described there would appear to be no doubt that the narcotic property of nutmeg is correctly attributed to myristicin, $C_{11}H_{12}O_3$, and it may be assumed that the latter substance when associated with the other constituents of the nutmeg is in a condition much more favorable for absorption than when in a pure state. As in the case of many other narcotics, the lower animals are much less sensitive than man to the direct action of nutmeg on the cerebral functions.

In conclusion, we desire to express our best thanks to Dr. H. H. Dale for having conducted the large number of physiological experiments involved in this investigation.

METHODS FOR PREPARING SOME PHARMACEUTIC CHEMICALS.

BY DR. GUNNAR HEIKEL.

ACIDUM HYDRIODICUM.

The official U. S. P. process for making this acid gives a product, which may be pure enough for most medicinal purposes, although it is far from being a chemically pure acid, owing to the fair solubility of potassium bitartrate in hydriodic acid, and to the addition of an appreciable amount of potassium hypophosphite. The allowable residue after evaporation, which according to the latest revision of the U. S. P. can be as high as 8.3 per cent., shows clearly that the degree of purity is very low indeed.

Another method for preparing diluted hydriodic acid, which is found in most of the text-books, is to conduct sulphuretted hydrogen gas into water in which iodine in fine subdivision is suspended. The reaction is thus:

$$I_2 + H_2S = 2HI + S$$

In the author's hands this method has proven unsatisfactory, as the iodine soon becomes entirely coated with the liberated sulphur and further action consequently ceases. If, however, the iodine be dissolved in carbon disulphide or chloroform, the solvent readily takes up the sulphur and the hydriodic acid goes into the supernatant water, which after separation from the solvent, is evaporated down to the desired concentration. The action of sulphuretted-hydrogen-gas upon a solution of iodine is also much more rapid than upon the iodine in solid form. Nevertheless, this method of preparation is slow, and the working with the bad-smelling sulphuretted hydrogen is very unpleasant. When a larger quantity of the acid is required the use of this method is almost out of question.

Hydriodic acid of a high degree of concentration, used, for example, as a reducing agent for organic compounds, is made by the action of phosphorus on iodine in the presence of water. The method being both tedious and expensive, and besides somewhat dangerous, is not suitable for pharmaceutical purposes.

A good, simple method for preparing an almost chemically pure acid, used in numerous instances by the author, is as follows: A solution of iron iodide is prepared in the usual way from iodine and iron-filings. To this solution somewhat more than the equiva-

lent quantity of pure precipitated barium carbonate is added, and the mixture boiled for 3–6 hours when the reaction: $FeI_2 + BaCO_3 \rightleftarrows FeCO_3 + BaI_2$ takes place. The equation is a reversible one, but proceeds from left to right in the beginning, much more rapidly than in the opposite direction, as in a state of equilibrium only a very small amount of iron iodide is present. According to the law of mass action the speed of a reaction is proportional to the concentration of the reacting substance. If therefore one of the products of a reversible reaction be removed, the reaction will go on in the direction to form more of that product. Hence, when ammonia, added to the filtered solution produces only a slight precipitate, which after prolonged boiling does not diminish, the equilibrium is reached, and the iron carbonate should be removed by filtration. The slight amount of barium carbonate in solution will usually be sufficient to precipitate the iron from the filtered solution, which, consequently, after cooling and standing for a few hours, becomes turbid, and after renewed filtration will be found perfectly free from every trace of iron. Should this not be the case, a further boiling with a little barium carbonate will throw out all the iron, and a solution of pure barium iodide will result.

This solution is now diluted to a definite volume and its strength accurately determined, which can be done by precipitating the barium with sulphuric acid and weighing the sulphate. The author prefers however to determine the iodine by the Volhard's method (the direct titration with potassium chromate as indicator can not be used on account of the insolubility of barium chromate), which is both rapid and very accurate. When the amount of barium iodide is known such a calculated quantity of a dilute (10–20 per cent.) exactly standardized sulphuric-acid solution is added as to cause an exact precipitation of the barium. The barium sulphate settles quickly, and if the strength of the solutions were accurately determined the resulting hydriodic acid solution gives only a slight precipitate either with sulphuric acid or barium chloride test solution. As barium as an impurity is more objectionable than sulphuric acid, the solution should be fixed by the addition of small amounts of sulphuric acid, so as to give just a very slight cloud with barium chloride test solution, when it is filtered or decanted and evaporated down to the desired concentration. The acid, which is decomposed to a slight extent, is decolorized by boiling it 10–15 minutes with a

small quantity of hypophosphorous acid (the solution should contain about 0.5 per cent. of the absolute acid). In this condition it will keep unchanged for more than a year.

The yield is quantitative provided that the precipitates are washed completely.

ACIDUM HYPOPHOSPHOROSUM.

The U. S. Pharmacopœia does not give any process for preparing this acid. An imperfect preparation may be made by using potassium hypophosphite and tartaric acid in the same manner as the potassium iodide was used in the manufacture of hydriodic acid. The National Dispensatory also suggests to make the acid from calcium hypophosphite by exact precipitation with oxalic acid. The resulting calcium oxalate, although insoluble in water, is, however, to a considerable extent, soluble in hypophosphorous acid. The acid prepared that way will consequently not stand the U. S. P. requirement of giving a clear solution after neutralizing with ammonia. Calcium oxalate as an impurity is really very objectionable, owing to its marked poisonous character.

It is evident that the best way to prepare hypophosphorous acid would be to decompose barium hypophosphite with the exact quantity of sulphuric acid. This salt is, however, about six times as expensive as the official potassium and calcium salts, and therefore the buying of the same for making hypophosphorous acid would not be economical.

The author uses the following method for preparing a solution of pure barium hypophosphite:

Calcium hypophosphite in solution is precipitated with somewhat more than the equivalent quantity of ammonium oxalate (prepared by neutralizing a solution of oxalic acid with ammonia water).

The reaction is thus:

$$Ca(H_2PO_2)_2 + (NH_4)_2C_2O_4 = 2NH_4H_2PO_2 + CaC_2O_4$$

The calcium is completely precipitated, the oxalate being perfectly insoluble in the neutral solution of ammonium hypophosphite (with the small excess of ammonium oxalate). The solution is filtered and the filtrate boiled with barium carbonate in excess, preferably under a hod, until the odor of ammonia has disappeared. The reaction is thus:

$$2NH_4H_2PO_2 + BaCO_3 = Ba(H_2PO_2)_2 + 2NH_3 + CO_2 + H_2O$$

The surplus of ammonium oxalate is also eliminated by the process, the reaction products being ammonia, carbonic acid and insoluble barium oxalate. To accelerate the reaction it is advisable to keep the mixture very concentrated, avoiding, however, an evaporation to dryness, which would cause a decomposition of the barium hypophosphite with evolution of the exceedingly poisonous phosphine-gas. When the reaction is complete the product is treated for a considerable time with a large amount of water, and filtered away from the surplus of insoluble barium carbonate and the small amount of barium oxalate. The strength of the barium hypophosphite solution is, after concentration, exactly determined and the decomposition with the calculated quantity of dilute sulphuric acid is conducted, preferably in boiling hot solution. The filtrate should be absolutely free from barium and give only a slight test for sulphuric acid.

BISMUTH SUBSALICYLATE.

As other metals with a weak positive nature, bismuth is characterized by the easy hydrolysis of its neutral salts, with formation of insoluble basic salts. Theoretically the bismuth hydroxide $Bi(OH)_3$ gives with the monobasic salicylic acid $C_6H_4OH\ COOH$ the following salts:

Neutral bismuth trisalicylate $(C_6H_4OH\ COO)_3Bi$ with an ignition residue of 37.9% Bi_2O_3.

Monobasic bismuth salicylate $(C_6H_4OH\ COO)_4Bi_2O$ with an ignition residue of 47.8% Bi_2O_3.

Dibasic—or bismuth subsalicylate $C_6H_4OH\ COO\ BiO$ with an ignition residue of 64.5% Bi_2O_3.

The National Dispensatory states that bismuth subsalicylate can be prepared by Duyk's process by shaking freshly precipitated bismuth hydroxide with salicylic acid in the presence of water. The author has tried the process, but even by using a large excess of salicylic acid, in order to get the benefit of the mass action, and shaking continuously for several days, the product when washed with hot water until free from salicylic acid, consisted mainly of the hydroxide with only a small amount of subsalicylate, showing that the action of the weak salicylic acid upon the insoluble bismuth hydroxide is very slight indeed. The dibasic salt must consequently

be prepared through the hydrolytic dissociation of the neutral salt just as the subnitrate precipitates out, by diluting a solution of bismuth-trinitrate.

The hydrolysis takes place according to the equation:

$$[C_6H_4(OH)COO]_3Bi + H_2O = C_6H_4OH\ COO\ BiO \\ + 2C_6H_4OH\ COOH$$

The actual course for preparing bismuth trisalicylate and effecting its subsequent hydrolysis is briefly as follows:

Metallic bismuth, or the subnitrate, is dissolved in nitric acid, care being taken to obtain a concentrated solution with a minimum amount of free acid. Into this an ammonium salicylate solution containing somewhat more than 3 molecules of salicylic acid to 1 atom of bismuth, is slowly poured, under constant stirring (both solutions have to be cold in order to avoid a pink coloration due to the oxidation of salicylic acid through the ammonium nitrate formed). At first salicylic acid precipitates out in quantity equivalent to the free nitric acid in the bismuth solution. After that the salicylic acid loosely combines with the bismuth, forming the unstable trisalicylate. Ammonium salicylate is added until no further precipitate is produced in the filtered solution.

In order to remove the bulk of the ammonium nitrate, the precipitate is poured upon a strainer and washed twice or thrice with cold water, after which it is transferred to a kettle, boiled with water, again strained and the operation repeated until the filtrate does not redden blue litmus paper.

The salt when dried at a low temperature is perfectly white, bulky, and conforms to all requirements of the U. S. Pharmacopœia. The salicylic acid is recovered from the wash water by concentration.

As the alkali salts of salicylic acid readily dissolve in water, it seems as if advantage could be taken of that property by using an alkaline solution for washing out the loosely combined salicylic aci l. This is, however, not advisable as even a very diluted alkali-solution readily decomposes the subsalicylate, while pure boiling water has no effect upon the same. By using for the first washing a sodium carbonate solution, in a quantity not sufficient to combine with all the salicylic acid present in excess of the subsalicylate, and washing until neutral with hot water, the product left by ignition 67.6% Bi_2O_3 showing that the carbonate already had acted upon some subsalicylate with formation of the hydroxide.

The bismuth salicylate with 40% Bi_2O_3 is as shown by the formulas not a definite compound, although the composition comes near to that of bismuth trisalicylate. After washing the bismuth trisalicylate with cold water until free from ammonium nitrate, an analysis will show if the product has to be further washed with hot water, or if salicylic acid should be added in order to obtain a salicylate with an ignition residue of 40% Bi_2O_3.

ZINC PERMANGANATE.

This is not an official preparation and its medicinal use is rather limited. No doubt the salt is a very good antiseptic and astringent and the publication of a cheap practical method for its preparation may therefore be of interest.

The National Dispensatory states that this salt may be made by exact precipitation of barium permanganate with zinc sulphate, but the barium salt is an expensive article, making the method impracticable unless it can be cheaply prepared. The author has manufactured a considerable quantity of zinc permanganate by the following process:

To a saturated solution of potassium permanganate the equivalent quantity of a concentrated silver nitrate solution is added. Sparingly soluble silver permanganate is precipitated at once according to the equation:

$$KMnO_4 + AgNO_3 = AgMnO_4 + KNO_3$$

The mixture is kept cold by addition of ice and left standing for a couple of hours to make the precipitation as complete as possible, after which the silver permanganate is filtered (preferably using a suction pump and berliner funnel) and washed with cold water until free from potassium nitrate. The pure silver salt is then dried below 100° C. The yield is about 80 per cent. of the theoretical quantity. To the washings which contain the rest of the silver, sodium chloride is added and the precipitated silver chloride collected by filtration.

The dry silver permanganate is accurately weighed, transferred to an evaporating dish, 5 to 8 times its weight of water added, and heated on a steam bath. To this the exactly equivalent quantity of pure zinc chloride is added and the whole heated with frequent stirring for a couple of hours.

The reaction is as follows:

$$2AgMnO_4 + ZnCl_2 = Zn(MnO_4)_2 + 2AgCl$$

When the reaction is thought to be complete, which can be judged by the disappearance of silver permanganate crystals, a few c.c. of the liquid are decolorized by heating with nitric acid and formaldehyde, divided in two portions and tested for silver or chlorides, respectively, with sodium chloride or silver nitrate test solutions. If the right amount of zinc chloride was added, the decolorized solution will, after completion of the reaction, give only a slight test either for silver or chlorides. If the former is present, a small amount of zinc chloride should be added and the heating continued until the solution gives just a slight test for chlorides. If the contents of zinc chloride is found to be too large, some silver permanganate, or if none of the same is at hand, some silver oxide, should be added until only traces of chloride are found in the zinc permanganate solution, which then is filtered from the silver chloride and evaporated to dryness on a steam bath. The yield of $Zn(MnO_4)_2$ $6H_2O$, is somewhat more than the potassium permanganate originally taken.

The collected silver chloride is reduced to the metallic state by means of zinc in a hydrochloric acid solution. The amount of silver recovered is quantitative, and if desired the original amount of silver nitrate can be restored by dissolving the metal in nitric acid, evaporating and crystallizing. The cost of the preparation will therefore not much exceed that of potassium permanganate.

It is evident that by decomposing silver permanganate with barium, calcium, magnesium, or other metallic-chlorides, the corresponding permanganates will result. Hence the barium permanganate, after having been prepared from the silver salt can be used, if so desired, for manufacturing other permanganates.

As a fact of curiosity rather than a matter of any practical value the author observed the interaction between manganese sulphate and barium permanganate. Theoretically a manganese permanganate $Mn(MnO_4)_2$ should be formed. Such a combination does not, at least under ordinary conditions, exist, the result of the reaction being a solution of permanganic acid with a precipitate of barium sulphate and manganese dioxide according to the equation:

$$3Ba(MnO_4)_2 + 3MnSO_4 = 3BaSO_4 + 5MnO_2 + 2HMnO_4$$

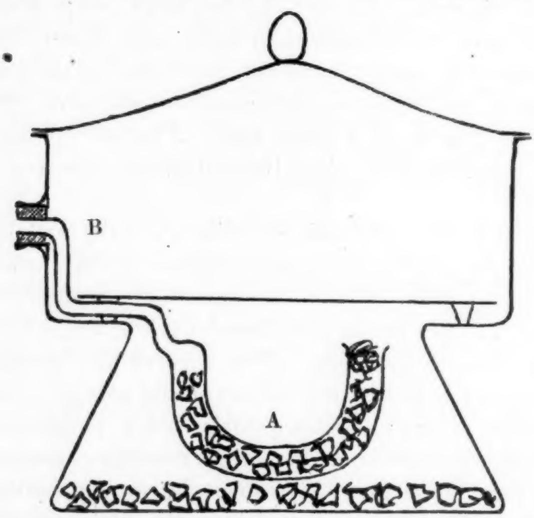
The reaction is remarkable in the respect, that an acid is formed through the interaction of two perfectly neutral salts.

EXPERIMENTAL LABORATORY OF THE NORWICH PHARMACAL COMPANY.

A PRESSURE EQUALIZING ATTACHMENT FOR DESICCATORS.

BY EDWIN DOWZARD.

Everyone has noticed the jump and side-slip of desiccator lids after placing hot crucibles or basins therein. This is of course caused by the expansion of the contained air, brought about by the hot article. When the contents of the desiccator have cooled there is a slight vacuum which renders the lid somewhat difficult to remove; when the lid has been removed there is a sudden inrush of



A. $CaCl_2$ tube charged with $CaCl_2$. B. Tube connecting U-tube with outside air.

air which does not improve the efficiency of the desiccator. These faults may be remedied in a very simple manner by the attachment illustrated in the sketch. The apparatus consists of a calcium chloride U-tube to which has been fused a piece of glass tubing bent to fit against the inside surface of the desiccator. The end of the tube passes through a perforated rubber stopper fitted in the neck. It will be seen that the U-tube charged with calcium chloride allows the expanded air to escape and also allows dry air to enter, thus keeping the air inside the desiccator at the same pressure as the surrounding atmosphere.

This apparatus has been in use for several years, giving perfect satisfaction.

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PROGRESS IN PHARMACY.

A QUARTERLY REVIEW OF SOME OF THE MORE INTERESTING LITERATURE RELATING TO PHARMACY AND MATERIA MEDICA.

By M. I. Wilbert, Washington, D. C.

The meetings of pharmacists and of druggists that were held in this country, in Canada and in England, during the past months, again evidenced the altogether too well established fact that the rank and file of the men connected with the drug trade, in English speaking countries, are altogether too apathetic to the progress that is going on about them. It is true that there is some indication that this apathy is gradually giving way to an awakening, by some, to live up to the duties that are involved and the responsibilities that are incurred by the vocation of their choice.

Compared with the intensity of interest that is manifested by the agricultural chemist, or the food and dairy commissioners, the interest that was manifested in the science of their calling, by American pharmacists or their English brethren, is not to be commended.

The twenty-fifth annual convention of the Association of Official Agricultural Chemists was held in the city of Washington, November 11 to 14, 1908. Apart from being an incentive to greater interest in the science of their own business, this meeting was of particular interest to pharmacists in that matters relating to drugs and medicines were given an unusual amount of attention, while pharmacopœial tests and requirements were discussed in a way that will surely be helpful in the future revisions of that book.

The shortcomings of the official assay methods were discussed at some length and the difficulty of obtaining concordant results was clearly evidenced. The reports of progress in several lines of investigative work gave promise of definite advances in the near future. One of the more interesting communications of the series on drugs and chemicals was a paper by Prof. Rusby, who pointed out very clearly the need for a wider conception in regard to the standards for drugs and demonstrated very clearly that chemical methods alone were far from being satisfactory in accurately estimating the efficiency, the identity or the purity of any given drug.

The First International Food Congress.—L. M. Douglas (*Pharm. Jour.*, London, Oct. 3, 1908, p. 437), in discussing the several prominent features of the first food congress, of an international character, points out that the value of any resolutions passed by this congress

must be considered as being, largely at least, of an academic character, inasmuch as the nation with a preponderance of delegates present must control the issues.

Gnomon (*Pharm. Jour.*, London, October 10, 1908), in discussing the same subject, asserts that "Congresses are being sadly overdone." He further discusses the attempts that were made to establish acceptable definitions for various food products and says: "It cannot be said that uniform success attended the efforts in this direction, for while some of the definitions recorded are obviously incomplete or wrong, others which were submitted proved to be of such limited applicability that no two manufacturers of certain articles could agree as to their fitness."

The next congress will be held in Paris, in 1909, and it is thought that a greater and more representative collection of delegates will assemble at that time and that more definite results may be expected.

The eightieth meeting of the German Naturalists and Physicians was held this year at Cologne, during the week following September 21.

The section on Pharmacy and Pharmacognosy was presided over by Dr. Frerichs, of Bonn. The program for this section was an unusually meagre one and included but three papers.

The International Congress on Tuberculosis, which was held in the city of Washington, during the week following September 28, 1908, has very properly been characterized as a convincing demonstration of the wide-spread interest in the tuberculosis problem and a most promising showing of the success that has attended the combating of this dread disease.

Not the least interesting portion of this congress was the exhibit, which demonstrated, as words never could, the work that is being done in all parts of the world to prevent infection, to recognize the disease at an early period so as to prevent its progress and, whenever possible, to effect a cure.

Next in importance to the several meetings and congresses that have been held, during the past three months, few occurrences have attracted more wide-spread attention than the publication of the new French Pharmacopœia.

French Codex.—According to the reviews that have appeared in the European pharmaceutical journals the new Codex is in many ways an improvement on its predecessor. The latter had 728 pages while the present edition has 999 pages. In the present edition the

monographs appear in alphabetical order, in place of being arranged in classes as formerly.

The provisions of the Brussels Conference for the unification of the formulæ of potent medicaments were generally included, the noteworthy exceptions being the standards for syrup of ferrous iodide and for mercurial ointment.

Among the newer remedies that have been included we find Adrenalin, Arrhenal, Aspirin, and Sodium Cacodylate.

Fluidextracts have also been included and are now represented by ten titles, including Frangula, Cascara, Ergot, Grindelia, and Hydrastis.

The serums include Antidiphtheritic, Antipest, Antistreptococcic, Antitetanic, and Antivenom.

The dilute acids and Aqua ammoniæ are now required to contain 10 per cent. of their respective constituents, and in this respect closely correspond to the requirements of our own Pharmacopœia. Altogether it may be said that the new French Codex is another step in advance, in matters pharmaceutic, and that the long wished for Universal Pharmacopœia, at least so far as the more active medicaments are concerned, is a possibility of the near future.

Postgraduate instruction in Switzerland has proven to be not alone feasible, but an accomplished fact; and, a rather unexpected success.

Following the course at the University of Bern (reported in this JOURNAL some months ago), a similar course was offered at the University of Zurich. The applications for this course were so numerous that despite the fact that three separate sections were organized, several of the applicants were compelled to wait the formation of a fourth section later in the year.

As at Bern earlier in the year the work was both didactic and practical, covering from seven to nine hours each day for ten days. The branches that were reviewed included sterilization, the use of indicators, alkaloidal assay methods, the estimation of iodine and saponification numbers, chemical composition of the newer remedies, the determination of the melting- and boiling-points, the use of the refractometer, and the use of the compound microscope.

Cleveland School of Pharmacy Affiliated with the Western Reserve University.—This item of news will undoubtedly please all who are in any way interested in the progress of education along pharmaceutical lines. As the pharmaceutical department of a

great and growing university the Cleveland School of Pharmacy will undoubtedly strive to emulate the example that has been set for it by the medical school of the same University, and we may reasonably expect that in the very near future the Cleveland school will be second to none in its requirements and in the character of its curriculum.

Council on Pharmacy and Chemistry.—The Journal of the American Medical Association (September 26, 1908, p. 1078) records an account of the meeting of the Council on Pharmacy and Chemistry which was held at the Association Building, Chicago, July 17 and 18, 1908. From this account it appears that as its chief business the Council discussed the revision of the rules and the rearrangement of the matter contained in "New and Non-official Remedies." It was decided that in future this book shall contain descriptions of the proprietary articles accepted by the Council and of such simple non-proprietary and unofficial substances as are of sufficient importance. It was decided that proprietary mixtures shall not be included in the main body of the book unless they show some originality and present a marked advance over similar products, but when they conform to the rules they shall be included in the form of an appendix to the book. Articles which are official in the "United States Pharmacopœia" or in the "National Formulary," and non-proprietary mixtures of official articles are not eligible for inclusion in the book. The rules (see *A. J. P.*, 1905) were modified in some minor particulars, the following modifications being of first importance:

Rule 5 was so amended as to require that the actual identity of the manufacturer of a product be furnished.

The Council voted to interpret Rule 8 so that after January 1, 1909, pharmaceutical preparations and mixtures will be admitted only under a pharmaceutical title which shall indicate the most potent ingredients. Arbitrary coined names will not be recognized for pharmaceutical mixtures.

It was also decided that no pharmaceutical mixture shall be accepted whose name indicates its therapeutic action or is suggestive of the names of diseases or pathologic conditions in which it is to be used. After January 1, 1909, this rule is to be extended to simple articles.

The Council voted to condense Rules 9 and 10 to become Rule 9 and adopted a new rule, as Rule 10, under which recognition will be

refused to articles, which, because of their unscientific composition, are useless or inimical to the best interests of the public or of the medical profession.

If these several rules of the Council, as amended, are carefully studied it will be found that they are designed to at least counteract, if they do not serve to eliminate, much of the secrecy and fraud that has served to bring discredit to American pharmacy and to convert the average medical practitioner into an unpaid peddler of nostrums.

The Council also endorsed the publication, in pamphlet form, of the series of articles, which had appeared in the *Journal of the American Medical Association,* entitled: "The Broader Aims of the Council on Pharmacy and Chemistry of the American Medical Association." This pamphlet, containing 48 pages of material, is now available and should be carefully studied by everyone interested in the progress of medical sciences in America.

The Committee of One Hundred of the American Association for the Advancement of Science has been actively agitating for an increase in the work done by the several Bureaus devoted to the promotion of the public health. Professor Irving Fisher, the president of the committee states (*Science,* Nov. 13, 1908, p. 676) that President Roosevelt has definitely taken up the program of the committee as part of his administration policy. He intends to incorporate the recommendation in his next message to Congress—that the health bureaus of the government be concentrated into a common department, from which the bureaus not consistent with health and education will be removed elsewhere. This will be the first and most important step toward a powerful department whose special interest will be health and education.

The Mann Bill.—H. R. Bill No. 21,982, which is designed to regulate and in a measure control interstate commerce in habit-forming and other noxious and potent drugs, has been freely criticised in medical as well as in drug journals during the past three or four months. The same measure was also vigorously denounced at the meeting of the National Wholesale Druggists' Association, at Atlantic City this year. While many if not all manufacturers and wholesale dealers will admit that something should be done to restrict the traffic in habit-forming drugs they nevertheless feel that the provisions of this particular bill are altogether too far-reaching and would tend to restrain and to interfere with legitimate trade

rather than regulate the illicit traffic in noxious or habit-forming drugs.

Patent Medicine Bill in Canada.—The law recently enacted in Canada to regulate the manufacture and sale of so-called patent medicines, embodies several features that promise to be efficient in controlling many of the abuses that have arisen from the promiscuous sale and use of the more or less harmful nostrums. The Canadian law provides that manufacturers must secure a license from the Minister of Inland Revenue and that when a compound contains one or more of a list of about thirty drugs the exact content of any of these drugs must be furnished. If the quantity is thought to be excessive or if the mixture as a whole otherwise objectionable, the license is to be withheld.

British Patent Law.—The *Pharmaceutical Journal* in discussing the practical working of the recently enacted patent law points out that a number of well known English firms are now preparing to manufacture some of the articles now patented in that country, when the patent rights, according to the new law, have elapsed. (*Pharm. Jour.*, London, Sept. 9, 1908, p. 319.)

A Botanical Garden at Johns Hopkins University has been provided for by the setting apart of two acres of ground, at the new site for such a purpose. On this ground it is proposed to erect a greenhouse and a laboratory for plant physiology. One and one-quarter acres of the land have been laid out in formal squares bounded by hemlock hedges, within which are beds and pools planted with some three hundred types illustrating the adaptation of vegetative organs of plants, the structure and cross pollination of flowers and the dispersal of fruits and seeds. (*Science,* Oct. 16, 1908, p. 511.)

Barium a Cause of the Loco-weed Disease.—Bulletin No. 29 of the Bureau of Plant Industry is devoted to a report of the work done by Crawford on the so-called loco-weeds of the western states. Crawford has found that certain plants, of themselves harmless, or even available as forage, when growing on certain soils, take up barium in quantities sufficient to cause either acute or chronic poisoning in live stock. This discovery is particularly surprising because of the fact that much time and thought has been expended on these so-called loco-weeds, in years gone by, with little or no practical results.

Poisoning by Bismuth Subnitrate.—In a recent number of the

Schweizerische Wochenschrift für Chemie u. Pharmacie (page 621) Dr. Fleissig comments on several cases of fatal poisoning that have followed the ingestion of large quantities of Bismuth subnitrate for diagnostic purposes in connection with the Röntgen rays.

He concludes that the poisoning was due to liberated nitrite compounds rather than the absorption of bismuth or to possible contamination, the theory being that the intestinal bacteria tend to decompose the nitrate with subsequent formation of nitrous acid.

Hypodermics of Iron in Tuberculous Anæmia.—Peters, in the *Medical Record,* says that excellent results can be obtained by hypodermic injections of iron, in cases of secondary anæmia accompanying tuberculosis. He uses a solution of iron citrate, with or without strychnine and sodium arsenate. (*J. Am. M. Assoc.,* Oct. 24, 1908, p. 1461.)

Commercial Thyroid.—Hunt and Seidell (*J. Am. M. Assoc.,* Oct. 24, 1908, p. 1385) point out that there is a great variation in the activity of the commercial preparations of thyroid. Thus, for instance, a so-called five-grain tablet of thyroid may contain but two grains of dried thyroid, so as to represent five grains of the fresh gland, or it may contain five grains of the dried gland and thus represent ten or more grains of the fresh substance.

Adulterated Gentian.—The adulteration of powdered gentian has been quite common, in England. As a ready means of differentiating between the true and the adulterated material, Wightman suggests a practical application of the faculty of the several components to absorb water. He points out that the genuine drug absorbs much more water than any of its adulterants and that when 8 or 10 grammes are placed in about 150 c.c. of water in a 200 c.c. graduate the sediment of the pure drug will measure much more than the corresponding sediment from an adulterated sample. (*Pharm. Jour.,* London, Aug. 29, 1908, p. 255.)

Caffeine-free Coffee.—Sendrich and Murdfield have analyzed fourteen samples of so-called caffeine-free coffee and ten samples of ordinary roasted coffee and have found that while the latter contained an average of 1.186 per cent. of caffeine the former averaged 0.218 per cent. or about one-sixth the amount present in ordinary coffee. (*Pharm. Jour.,* Oct. 10, 1908, p. 464, from *Zeitschr. f. Unters. Nahr. u. Genussmittel.*)

Deterioration of Fluidextracts.—Dr. William Jay Schieffelin reports that from tests conducted in the laboratory of Schieffelin &

Co. it was found that fluidextract of aconite deteriorates 10 per cent. and fluidextract of hyoscyamus 9 per cent. in the course of a year. A number of other fluidextracts that were under observation showed practically no deterioration during the same period of time. (*Am. Drug.*, Oct. 26, 1908, p. 264.)

New Reagent for Morphine and Oxydimorphine.—Sodium molybdate 0.15 Gm., formaldehyde solution 35 per cent., 10 drops, and strong sulphuric acid 30 c.c. are freshly mixed. The reagent so obtained is very sensitive to morphine and especially to oxydimorphine. With the latter it gives at first a violet color then suddenly a bluish-green which disappears on dilution with water. With morphine the violet color at first obtained becomes bluish violet and finally a dull green. (*Pharm., Jour.*, Oct. 3, 1908, p. 434, from *P. J. Jap.*)

Allophan.—This is said to be the allophanic acid ester of santalol and it is claimed to contain 72 per cent. of santalol. It is further said to be similar to santalol in its action but to be entirely devoid of any tendency to irritate. (*Pharm. Ztg.*, Sept. 30, 1908, p. 778.)

Almatein.—This is said to be a condensation product of hæmatoxylon and formaldehyde. It is directed to be given, internally, in diarrhœas of children and in dysentery as an astringent and externally as an antiseptic dressing. (*Pharm. Ztg.*, 1908, Sept. 30, p. 778.)

Aperitol is said to be valeryl-acetyl phenolphthalein. It is recommended as an aperient in doses of 0.2 Gm. (*Pharm. Ztg.*, 1908, Sept. 30, p. 778.)

Arsacetin is the name given to sodium para-acetylamino-phenylarseniate, the equivalent of an acetyl combination of atoxyl. This compound is stated to be five times less toxic than arsenites and may be given in nervous affections and in anæmia in doses of from 0.1 to 0.2 and even 0.5 Gm. by gradual increase of hypodermatic injections. (*Pharm. Jour.*, London, Sept. 12, 1908, p. 302, from *Pharm. Ztg.*)

Beta Eucaine Lactate.—Chemically this is the lactate of benzoylvinyl-diaceton alkamine. It occurs as a white crystalline powder soluble in water at the ordinary temperatures to about 22 per cent., in alcohol to about 11 per cent., in chloroform to about 20 per cent. Its uses are the same as Beta eucaine hydrochloride over which it has the advantage of greater solubility. (*J. Am. M. Assoc.*, Oct. 17, 1908, p. 1337.)

Diplosal.—This is said to be the salicylic acid ester of salicylic acid or salicylosalicylic acid. It is being recommended as a substitute for salicylic acid in cases of acute articular rheumatism. Dose 1 Gm., or daily doses of from 5 to 6 Gm. (*Pharm. Ztg.*, Sept. 30, 1908, p. 778.)

Eulaxans is being exploited as an aperient. It is said to consist of one molecule of phenolphthalein and 2 molecules of sodium hydroxide. (*Pharm. Ztg.*, Sept. 30, 1908, p. 778.)

Euphyllin is the name given to a compound of theophylline with ethylene diamine. The new compound is a crystalline product consisting of a mixture each gramme of which corresponds to 0.82 grammes of theophylline. (*Pharm. Jour.*, Sept. 5, 1908, p. 280, from *Therap. Monatsh.*)

Iodalbin.—This is the name given to a compound of iodine and blood albumin and containing approximately 21.5 per cent. of iodine. It is recommended as a substitute for the soluble alkaline iodides. May be given in doses of from 0.30 to 0.60. (*J. Am. M. Assoc.*, Oct. 24, 1908, p. 1427.)

Iodothyrin.—Hunt and Seidell (*Jour. Am. M. Assoc.*, Oct. 24, 1908, p. 1388) point out that the commercial preparation bearing this name evidently varies more or less in composition. This variation was evidenced both by chemical and physiologic tests.

Lecebrin is the name given to a preparation of lecithin from the brain in combination with nucleoprotëins, containing 33⅓ per cent. by weight of lecithin. (*Jour. Am. M. Assoc.*, Oct. 24, 1908, p. 1427.)

Novaspirin Quinine.—On mixing ethereal solutions of quinine and of novaspirin, in their molecular proportions, combinations corresponding to an acid and to a basic salt of quinine with citrosalicylic acid may be obtained. The former contains about 18 per cent. and the latter 34 per cent. of quinine. Both salts are insoluble in water but soluble in alcohol and in chloroform. (*Pharm. Jour.*, London, Oct. 10, 1908, p. 464, from *Boll Chim. Farmac.*)

Panase is the name given to a combination of digestive enzymes of the pancreas derived from the pancreatic gland of the pig. It occurs as a light yellowish powder having a slight odor and somewhat mucilaginous taste. It is incompatible with strong alcohol, acid alkalies and other substances which tend to destroy the activity of ferments. It is given in doses of 0.13 Gm. or more. (*Jour Am. M. Assoc.*, Oct. 31, 1908, p. 1513.)

Phenol Tablets.—Under this name a firm in Germany is now marketing a compressed tablet containing the oxalic acid ester of phenol. This substance contains 32 per cent. of oxalic acid and 68 per cent. of phenol, has a melting-point of from 122° to 124° C., is non-hygroscopic, practically non-caustic and, on solution, dissociates into its constituents. (*Pharm. Centh.*, 1908, p. 797.)

Spirosal is defined by the Council on Pharmacy and Chemistry of the American Medical Association as the monoglycol ester of salicylic acid. It occurs as an almost odorless and colorless oily fluid, easily soluble in alcohol, ether, chloroform and benzol and soluble in about 110 parts of water and in 8 parts of olive oil. It is recommended to be used externally in rheumatic affections. (*Jour. Am. M. Assoc.*, Oct. 31, 1908, p. 1513.)

Tannyl.—This occurs as a yellowish-gray, odorless and practically tasteless powder containing about 50 per cent. of tannin in combination with oxychlor casein. It is only very slightly soluble in water or in alcohol, but is readily soluble in alkaline solutions. It has been recommended as an internal astringent.

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